Clearance of 177Lu-DOTATATE from patients receiving peptide receptor radionuclide therapy

Experiences at the Royal Liverpool University Hospital

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Neuroendocrine tumours

Neuroendocrine tumours (NETs) are a heterogeneous group of tumours that stem from the endocrine system and express somatostatin receptors (SSTRs). The management of such tumours often begins with surgical resection of the primary tumour and can also include chemotherapy and external beam radiotherapy. Chemotherapy itself has a limited effect, showing a response of 20-35% in a small number of patients with poorly differentiated NETs and no effect whatsoever in those with well differentiated NETs. On the other hand, external beam radiotherapy is limited by the radiation dose deposited in healthy tissue, due to the disseminated nature of NETs.

Peptide receptor radionuclide therapy

Achieving the specificity required to provide the maximum tumour dose while sparing healthy tissue has been achieved through various modes of peptide receptor radionuclide therapy (PRRT). PRRTs rely on the combination of a suitable therapeutic isoanologue with a somatostatin analogue. The earliest applications of PRRT employed high doses of 111In-DTPA-octreotide (Octreoscan) to facilitate a response attributed to Auger and conversion electrons emitted by 111In. However, the relatively low abundance of electrons emitted and short path lengths emitted by 111In meant this type of therapy was only suitable in the treatment of very small tumours with a high uptake. Based on this, new somatostatin analogues have been developed that can be labelled with specific beta emitters producing electrons of higher energy and subsequently longer path length. Two of the most commonly employed beta emitters currently in use are 90Y and 177Lu. With maximum beta emissions of 2.27MeV and 0.49MeV respectively, path lengths of up to 10mm and 3mm can be achieved in tissue. Consequently, combinations of somatostatin analogues with 177Lu are better suited to patients with smaller tumours, and 90Y to those with larger tumours. In addition to the betas, 177Lu also has two gamma emissions at 133keV (6.5%) and 208keV (11%), providing a valuable tool in post-therapeutic imaging and a challenge in terms of external dose rate.

Somatostatin analogues themselves have also undergone significant development, particularly with respect to their affinity to SSTR subtype 2 (SSTR-2), the most densely expressed SSRT subtype in NETs. This has led to the clinical implementation of ligands such as DOTATOC and DOTATATE. DOTATOC and DOTATATE have demonstrated a nine-fold increase in uptake when compared to DOTATOC, based on its increased affinity to SSTR-2.

PRRT in Liverpool

The Royal Liverpool University Hospital (RLUH) is a European Neuroendocrine Centre of Excellence and has been offering PRRTs for over nine years. Patients currently receive a fractionated therapeutic dose of 90Y-DOTATATE or 177Lu-DOTATATE based on the size of their largest tumour. They are treated on inpatient basis, those receiving 90Y-DOTATATE being discharged after 24 hours and those receiving 177Lu-DOTATATE after 48 hours to take account of the extended physical half-life.

The aims of this work

The RLUH is one of only nine centres in the UK offering 177Lu-DOTATATE therapy, and one of only four offering 90Y-DOTATATE therapy. In this way the RLUH is able to accept referrals for PRRT from all over the UK. However, due to ever increasing referral rates, meeting the UK Department of Health’s 31-day standard for treatment is proving a significant challenge.

As a result, work is now underway aiming to evaluate whether it is necessary to keep 177Lu-DOTATATE patients in for the full 48 hours, whether they can leave after 24 hours or even the potential to treat on an outpatient basis. In making such an evaluation, two key considerations need to be taken into account:

1. The external dose rates during the first 48 hours post-administration;
2. The potential for contamination during this period.

If these considerations can be successfully addressed then the impact will not just be on the departmental waiting list, but also the patient experience.

External dose rates

In addressing the first of these two points, a group of patients have been subject to a dose rate analysis during their stay. This included measurements 1m from the trunk it can be seen that the dose rate falls off rapidly over the first 24 hours, more than likely due to rapid biological clearance (Table 1).

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>0h</th>
<th>4h</th>
<th>24h</th>
<th>45h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Rate (μSv.hr⁻¹)</td>
<td>29.8±10.8</td>
<td>21.7±3.4</td>
<td>8.0±3.0</td>
<td>6.2±1.7</td>
</tr>
</tbody>
</table>

TABLE 1

Mean (±1SD) 1m dose rates measured from a group (n=14: 8M, 6F) of 177Lu-DOTATATE patients during their inpatient stay at the RLUH

It can be seen that the dose rate at four hours is less than that estimated for a typical thyrotoxicosis patient immediately after an 800MBq therapeutic dose of 131I (~40μSv.hr⁻¹). Although this indicates that there is potential to manage these external dose rates, it should be noted that the thyrotoxicosis advice issued in the Medical and Dental Guidance Notes takes into account subsequent biological clearance of 131I. This is something that 177Lu-DOTATATE has already been subject to at this particular time point.

The potential for contamination

In addressing the potential for contamination, bi-exponential fitting has been performed on integrated (one minute) count rate measurements made using a RadHound scintillation counter (Southern Scientific) at equivalent times to those of the dose rate measurements above. The mean fit is illustrated in Figure 1 alongside measurements made from a group of patients administered with 90Y-DOTATATE (n=9).
The difference in biological clearance between $^{90}$Y-DOTATATE and $^{177}$Lu-DOTATATE patients illustrates an additional reason as to why the latter patients are subject to a longer hospital stay. Here it can be seen that by 24 hours the $^{90}$Y-DOTATATE group have excreted over 88% of their administered activity, whereas the $^{177}$Lu-DOTATATE group have only excreted 70%. The impact of this is such that over the next 24 hours the $^{177}$Lu-DOTATATE patients typically excrete a further 12% of their administered activity (~0.9GBq), compared to 7% (0.4GBq) for $^{90}$Y-DOTATATE patients.

It is also notable that the standard deviations at each time point, illustrated by error bars in Figure 1, are significant. This is something to be expected when it is considered every patient has a different tumour burden. This is particularly so for the $^{177}$Lu-DOTATATE patients, demonstrating variations of $\pm 20.5\%$, $\pm 9.8\%$ and $\pm 7.0\%$ at 4, 24 and 48 hours respectively. The decrease in this spread with time demonstrates that it is indicative of patient specific retention, and is further reflected by the reduced spread among the more rapidly clearing $^{90}$Y-DOTATATE patients. Here, the percentage retentions are seen to vary by $\pm 15.8\%$, $\pm 6.5\%$ and $\pm 2.7\%$ at 4, 24 and 48 hours respectively.

**Conclusions**

Ultimately this has illustrated that the external dose rates 1m from $^{177}$Lu-DOTATATE patients are manageable when considering same-day or next-day discharge. This should be done by issuing revised restrictions, which also take into account the fact that there is an increased likelihood of contamination by moving to an earlier time point in the post-therapy phase.

Clearly moving discharge earlier increases the range of external dose rates from this type of patient, and the range of activities excreted when this type of patient returns home. It is anticipated that this could be addressed with stratified advice that takes into account each patient’s specific retention at discharge.

**Moving forward**

It is anticipated that in the future a decision can be made before each treatment fraction regarding each patient’s eligibility for early discharge. This decision (Figure 2) could take into account their home circumstances; their ability to return for imaging and their health.

With the patient subject to regular imaging (Figure 3) as part of a process of dosimetry, the potential to use a four-hour whole body acquisition as an indicator of the required level of advice has begun to be investigated.

**FIGURE 1**
Mean percentage retention based on count rate measurements made at approximately 0h, 3h, 20h, 24h, 27h, and 45h post administration. The error bars are representative of ±1SD.

**FIGURE 2**
Possible decision tree addressing the eligibility of a patient for a shorter stay.
Although too early to make any firm conclusions, there is some indication that that the 24-hour, 48-hour and seven-day retentions can be estimated from a four-hour acquisition (figure 4). It is hoped that, based on this, a level of established stratified advice could then be issued to the patient. This would enable the patient to return home earlier without being subject to excessive “broad brush” restrictions.

References
3. IPEM, Medical and Dental Guidance Notes.